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ORIGINAL ARTICLE

Can serum free fatty acids assessment predict severe preeclampsia?

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KEYWORDS

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Abstract *Objective:* To estimate the relation between serum free fatty acids (FFAs) and severe preeclampsia in Egypt.
Methods: Twenty cases with severe preeclampsia (blood pressure ⩾ 160/110 after 20th week of gestation and proteinuria ⩾ 2.5 gm/24 h urine) were matched with 20 normotensive pregnant controls for age, and BMI. All study participants were registered to Elshatby Maternity University Hospital within a period of 10 months. Evaluation of serum fasting FFAs, uric acid, liver transaminases (AST, ALT) during delivery were done.
Results: The mean level of FFAs was significantly elevated in preeclampsia cases compared to women with normal blood pressure (2.12 ± 2.64, 0.43 ± 0.29 respectively, $p = 0.003$). Also, cases with high FFAs levels had significant increased levels of serum uric acid than control women with normal blood pressure (6.38 ± 1.25, 5.05 ± 1.85 respectively, $p = 0.006$). Women with high levels of serum FFAs had more than two folds increased risk for neonatal admission to Neonatal Intensive Care Unit OR (2.4).
Conclusion: This study suggests that elevated total serum FFAs might be an associated predisposing factor with preeclampsia in non-obese pregnant women.

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1. Introduction

Preeclampsia (PE) is a common pregnancy disorder that is diagnosed by new-onset gestational hypertension after the 20th week of gestation and proteinuria (BP 140/90 mm Hg or greater at least on two occasions, six or more hours apart, proteinuria ⩾ 300 mg/24 h or ⩾1+ by dipstick.[1] It is responsible for approximately 50,000 maternal deaths yearly worldwide, 25% of all cases of fetal intra uterine growth restriction (IUGR) and 15% of preterm births in developed countries.[2–4] Preeclampsia is the most common dangerous

pregnancy complications; affecting the mother and the fetus.[5] It is associated with an increased risk of cardiovascular disease and type 2 diabetes in later life of the mother.[6–10] There is no known cure for preeclampsia except delivery of the placenta. Consequently, early diagnosis of preeclampsia and close observation are imperative.

Many theories have attempted to explain why preeclampsia arises.[11] The mechanism causing preeclampsia is not totally understood. Much attention has been focused on the actual physiological changes of preeclampsia which may provide a better understanding of the disease process. Poorly functioning endothelial cells, the cells lining the inside of blood vessels, may be responsible for the physiologic changes of preeclampsia as it can become dysfunctional altering lipid peroxidation which is the process of converting unsaturated fatty acids in cells and tissues. Lipid peroxidation plays a role in the development of cardiovascular disease. There is increase in the oxidative stress during pre-eclampsia and as a consequence it leads to increased creation of lipid peroxides, reactive oxygen species and leading to endothelial injury and dysfunction. There is some evidence that preeclampsia patients have higher amounts of the by-products of lipid peroxidation.[12,13] Free fatty acids which also called non-esterified fatty acids (NEFAS) are fatty acids that are not esterified to glycerol or another alcohol such as choline or cholesterol. In blood plasma or serum, FFAs are really not free but bound to plasma albumin. Circulating free fatty acids (FFAs) are key regulators of glucose metabolism and have been shown to be increased in preeclamptic patients during and before the clinical onset of the disease.[12–14] It was hypothesized that alterations in the circulating lipids contribute in inducing endothelial dysfunction in patients with preeclampsia.

Therefore, the aim of this study was to estimate the relation between serum free fatty acids (FFAs) and severe preeclampsia.

Our study may be the first to examine the relation between serum FFAs and severe preeclampsia in Egyptian women.

2. Methods

2.1. Study design

We conducted a case control study of nulliparous non-obese pregnant women (BMI $< 30 kg/m^2$) aged 20–30 years. Twenty cases with severe preeclampsia (blood pressure $\geqslant 160/110$ after 20th week of gestation and proteinuria $\geqslant 2.5$ gm/24 h urine) were matched with 20 normotensive pregnant controls as regard age, and BMI. Severe preeclampsia was defined by any of the following criteria after 20 weeks gestational age: BP $\geqslant 160/110$ mm Hg after 20 weeks gestation on two or more occasions at least 6 h apart, proteinuria $\geqslant 5$ g/24 h, or $>2+$ on a voided sample, renal insufficiency (serum creatinine > 1.2 mg/dl unless known to be previously elevated), liver affection (elevated ALT and AST), neurological and hematological disturbance (platelets $< 100{,}000/mm^3$), and microangiopathic hemolysis.[15] All study participants were registered to El Shatby Maternity University Hospital between July 2009 and April 2010.

2.2. Measures

Upon approval from the research ethics Committee all participants signed informed consent. Blood pressures were calculated from the average of at least three blood pressure readings (Kortokov V, seated position) using standard cuffs for all women fitted with mercury sphygmomanometer to minimize the variations in measurement. Urine specimens were taken from each woman during delivery in a clean container to be checked for albumin using clicheck 10 teco urine reagent strips.

Evaluation of serum fasting FFAs, uric acid, AST, ALT during delivery were done for all study participants. The concentration of free fatty acids in the serum was measured by an enzymatic colorimetric method using NEFA-HR(2) colorimetric assay kit (Wako Chemicals GmbH, Germany).[16]

2.3. Data collection

Data were gathered from women who delivered in addition to their caring obstetricians involved as well as reviewing their medical records.

2.4. Statistical analysis

Data were analyzed using SPSS version 13. Differences between means for quantitative variables were tested by using independent t test. Differences in numbers for qualitative variables were tested by using X^2 or Fisher Exact test. Level of significance equal to 0.05 was used to determine statistical significance.

3. Results

This is a case control study of non-obese (BMI $< 30 kg/m^2$) pregnant women aged 20–30 years. Twenty cases with severe preeclampsia (blood pressure $\geqslant 160/110$ after 20th week of gestation and proteinuria $\geqslant 2.5$ gm/24 h urine) were matched with 20 normotensive pregnant controls for age, and BMI (Table 1). Table 1 shows a statistical significant difference

Table 1 Characteristics of women with severe preeclampsia and Normotensive women.

Characteristics	Cases of severe preeclampsia ($n = 20$)	Normotensive control ($n = 20$)	p
Maternal age (y)	26.40 ± 3.39	25.15 ± 2.60	0.098 NS
BMI (kg/m^2)	27.09 ± 2.13	26.30 ± 2.47	0.198 NS
Weeks of gestation at delivery	36.05 ± 1.15	38.60 ± 1.19	0.001[a]
Neonatal birth weight (gm)	2500 ± 700	3500 ± 850	0.001[a]

Data are shown as mean ± SD, BMI: body mass index, NS: not significant.
[a] Significant.

Table 2 Comparison of women with severe preeclampsia and Normotensive women according to mode of delivery, intra uterine growth retardation (IUGR), and foetal admission to NICU.

Characteristics	Cases of severe preeclampsia (n = 20) (%)	Normotensive women (n = 20) (%)	p
Mode of delivery Caesarean	13 (65)	6 (30)	0.027
IUGR	6 (30)	0 (0)	0.02[a]
Admission to NICU	9 (45)	5 (25)	0.187 NS

Data are shown as mean ± SD, NS: not significant, NICU: Neonatal Intensive Care Unit.
[a] Significant.

Table 3 Comparison of women with severe preeclampsia and Normotensive women according to serum FFA, serum uric acid, and serum transaminases (AST, ALT).

	Cases of severe preeclampsia (n = 20)	Normotensive women (n = 20)	p
Free fatty acids (mmol/l)			
Min–Max	0.32–7.5	0.02–1.2	0.003[a]
Mean ± SD	2.12 ± 2.46	0.43 ± 0.20	
Uric acid level (mg/dl)			
Min–Max	3.5–7.8	2.4–8	
Mean ± SD	6.38 ± 1.25	5.05 ± 1.85	0.0062[a]
AST			
Min–Max	12–42	10–42	
Mean ± SD	32.05 ± 7.16	19.5 ± 8.70	0.001[a]
ALT			
Min–Max	24–48	24–60	
Mean ± SD	34.75 ± 6.80	33 ± 9.75	0.275

Data are shown as mean ± SD.
[a] Significant.

between the preeclampsia cases and the normotensive control regarding the gestational age at delivery (p = 0.001). Also, we found that pre eclampsia cases had significant lower birth weight infants than the control (p = 0.001) (Table 1).

Caesarean section rate was significantly higher among preeclampsia women (65% versus 30%; p = 0.03) (Table 2). The mean gestational age for vaginal delivery was 37 ± 0.15 weeks and for the Caesarean section 36 ± 0.15 weeks. The crucial point in deciding between vaginal delivery and CS was the success in the control of the manifestations of severe PE within 24 h period and the presence of obstetric indication of CS as primi breech or fetal distress.

There were six cases of severe preeclampsia had babies with symmetrical IUGR compared to none of the normotensive controls (Table 2). Women with preeclampsia had more than two folds increased risk for neonatal admission to Neonatal Intensive Care Unit OR (2.4), 95% (CI) 0.64–9.39, p = 0.2 (Table 2).

Table 3 shows the comparison between the two studied groups as regards the total serum FFAs in mmol/litre. The serum levels of FFAs in women with severe preeclampsia ranged between 0.32 and 7.5 mmol/litre with a mean of 2.12 ± 2.64 mmol/litre. But, among normotensive control women, plasma FFAs ranged between 0.02 and 1.2 mmol/litre with a mean of 0.43 ± 0.29 mmol/litre. The mean level of FFAs was significantly elevated in preeclampsia cases compared to control women with normal blood pressure (p = 0.003). Moreover, cases with high serum FFAs levels (preeclampsia cases) had significant increased levels of serum uric acid than pregnant women with normal blood pressure (6.38 ± 1.25, 5.05 ± 1.85 respectively, p = 0.006). Serum AST was significantly higher in the preeclamptic patients compared to normotensive pregnant women (Table 3). On the contrary, there was no statistical significant difference between the two groups as regard serum haemoglobin and serum levels of ALT (Table 3).

4. Discussion

The present study was planned to assess the relation between serum total FFAs concentrations and severe preeclampsia in a case control study. We found that non-obese women with severe preeclampsia had significant higher levels of total serum FFAs when compared to normotensive pregnant women. Although our study may be the first to examine the relation between serum FFAs and severe preeclampsia in Egyptian women, our results were similar to other studies that have shown high levels of serum FFAs in cases with preeclampsia compared with normal pregnancy.[17,18]

Nicola et al. found that plasma from women with preeclampsia had increased lipid accumulation and endothelial apoptosis compared with plasma from women with uncomplicated pregnancies. They provide evidence that these changes potentially result from elevated concentrations of free fatty acids and increased its molar ratio to albumin. Also, they

had shown that plasma from women with preeclampsia had a significant impact on endothelial cellular metabolism and apoptosis compared with normal pregnant controls. They confirmed that exposure of endothelial cells to the 'preeclampsia' fatty acid/albumin combination, in comparison to the 'normal pregnant' cocktail of fatty acids and albumin, mimicked these impaired outcomes, which justify suggesting that circulatory levels of fatty acids in women with preeclampsia may be capable of affecting the properties of vascular endothelial cells.[17]

Similarly, Villa et al. found that total FFA and individual FFAs (arachidonic, linoleic, oleic and palmitic acids) were considerably higher in women with preeclampsia than in normotensive pregnant women; he also found no relationship between total FFA concentration and insulin sensitivity.[18] This was so in spite of the fact that preeclampsia is characterized by increased insulin resistance and increased adrenergic activity which was associated with increased lipolytic activity, which could underlie the increased circulating levels of FFA in pre-eclamptic women.[18–20] It is unknown which single FFA is attributed to the cause of preeclampsia but assessment of total serum FFAs in this study may serve as a proxy measure for the disturbed metabolism seen in preeclamptic women. Thus, in cases with severe preeclampsia the increased levels of serum FFAs may represent a predisposing factor. Subsequently, the high levels of FFAs can be attributed to several mechanisms: for example dietary intake may be suggested because preeclampsia occurs more in people with low socioeconomic class who have bad dietary habits. Meanwhile, a little is known about Egyptian dietary habits. Additionally, future studies are needed to understand whether or not women with severe preeclampsia have disturbed gastrointestinal absorption of fatty acids.

In our study we found that six women of preeclamptic group had babies with IUGR equal 30% of cases, meanwhile no one of the controls had babies with IUGR. Our study results were similar to studies done by Alvino et al. and Cetin et al. have studied total plasma fatty acid concentrations in maternal and fetal plasma in pregnancies complicated by intrauterine growth restriction (IUGR) and in pregnancies with both IUGR and preeclampsia.[1,21] Alvino reported total free fatty acid concentrations significantly higher in pregnancies with IUGR and IUGR accompanied with preeclampsia compared to controls.

Furthermore, we found that the mean serum uric acid values were significantly elevated in preeclampsia (6.38 ± 1.25 mg/dl) compared with normal pregnancy (5.05 ± 1.85 mg/dl) $p < 0.05$. Similarly, Tsukimori et al. (2008) found that the mean serum uric acid values were significantly elevated in preeclampsia (6.6 ± 1.5 mg/dl) compared with normal pregnancy (4.0 ± 0.7 mg/dl) ($p < 0.001$).[22] Also, we found that AST level was higher in preeclamptic women than in women with normal pregnancy.

This study suggests that elevated total serum FFAs might be a predisposing factor for preeclampsia in non-obese pregnant women (a known risk factor for cardiovascular diseases). Subsequently, this study might be used in future studies to prevent excessive cellular non-esterified fatty Acids to reduce the development or progression of preeclampsia.

One limitation of this study was the lack of evaluation of individual FFAs including arachidonic acid that can be a direct trigger to the occurrence of preeclampsia. Second, the study might need to be done on overweight women and further studies of detailed Egyptian dietary intake needs to be done. Also, the obtained data should be confirmed by further study on a large scale of patients. Finally, the specific study population may not represent women with more culture diverse population.

References

1. Alvino G, Cozzi V, Radaelli T, Ortega H, Herrera E, Cetin I. Maternal and fetal fatty acid profile in normal and intrauterine growth restriction pregnancies with and without preeclampsia. *Pediatr Res* 2008;**64**:615–20.
2. Roberts JM. Pregnancy related hypertension*Maternal Fetal Medicine*. 5th ed. p. 833–72.
3. Duley L. Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *Br J Obestet Gynaecol* 1992;**99**:547–53.
4. Goldenberg RL, Rouse DJ. Prevention of premature births. *N Engl J Med* 1998;**339**:313–20.
5. Lorentzen B, Endresen MJ, Clausen T, Henriksen T. Fasting serum free fatty acids and triglycerides are increased before 20 weeks of gestation in women who later develop preeclampsia. *Hypertens Pregnancy* 1994;**13**:103–9.
6. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129, 290 births. *Lancet* 2001;**357**:2002–6.
7. Pell JP, Smith GC, Walsh D. Pregnancy complications and subsequent maternal cerebrovascular events: a retrospective cohort study of 119, 668 births. *Am J Epidimiol* 2004;**159**(4):336–42.
8. Leik CE, Walsh SW. Linoleic, but not oleic acid upregulate production of interleukin-8 by human vascular smooth muscle cells via rachidonic acid metabolites under conditions of oxidative stress. *Reprod Sci* 2005;**12**(8):593–5.
9. Rodie VA, Freeman, Sattar N, Greer IA. Preeclampsia and cardiovascular disease: metabolic syndrome of pregnancy. *Atherosclerosis* 2004;**175**(2):189–202.
10. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Preeclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;**35**:974.
11. Courtney R, Williams C, Mabie, Baha M, Sibai. Pregnancy-Hypertensive disorders. *Armenian Med Netw* 2006.
12. Kashinakunti SV, Sunitha H, Gurupadappa K, Shankarprasad G, Suryaprakash G, Ingin JB. Lipid peroxidation and antioxidant status in preeclampsia. *Al Ameen J Med Sci* 2010;**3**(1):38–41.
13. Hubel CA, McLaughlin RW, Evans BA, Hauth CJ, Sims JM. Fasting serum triglycerides, free fatty acids, and malondialdehyde are increased in preeclampsia, are positively correlated, and decrease within 48 h post partum. *Am J Obstet Gynecol* 1996;**174**:975–82.
14. Murai JT, Muzykanskiy E, Taylor RN. Maternal and fetal modulators of lipid metabolism correlate with the development of preeclampsia. *Metabolism* 1997;**46**:963–7.
15. MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. *Obstet Gynecol* 2001;**97**(4):533–8.
16. Schimizu S, Tani Y, Yamada H, Tabata M, Murachi T. Enzymatic determination of serum free fatty acids: a colorimetric method. *Anal Biochem* 1980;**107**(1):193–8.
17. Nicola J, Robinsona L, Laura J, Minchella, Myersa JE, Carl A, Crockera LP. A potential role for free fatty acids in the pathogenesis of Preeclampsia. *J Hypertens* 2009;**27**:1293–302.
18. Villa PM, Laivuori H, Kajantie E, Kaaja R. Free fatty acid profiles in preeclampsia. *Prostaglandins Leukot Essent Fatty Acids* 2009;**81**:17–21.

19. Kaaja R, Laivuori H, Laakso M, Tikkanen MJ, Ylikorkala O. Evidence of a state of increased insulin resistance in preeclampsia. *Metabolism* 1999;**48**:892–6.
20. Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia a state of sympathetic overactivity. *N Engl J Med* 1996;**335**:1480–5.
21. Cetin I, Giovannini N, Alvino GC, Agostoni, Riva E, Giovannini G, Pardi G. Intrauterine growth restriction is associated with changes in polyunsaturated fatty acid fetal–maternal relationships. *Pediatr Res* 2002;**52**:750–5.
22. Tsukimori K, Tomoyuki Yoshitomi T, Seiichi Morokuma S, Kotar Fukushima K, Wake N. Serum uric acid levels correlate with plasma hydrogen peroxide and protein carbonyl levels in preeclampsia. *Am J Hypertens* 2008;**21**(12):1343–6.